APPENDIX D:
CLAIMS OF THE PRESENT APPLICATION CORRESPONDING TO THE PROPOSED COUNT

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
195. A method of inhibiting B lymphocytes comprising administering an effective amount of an antibody that binds a protein whose amino acid sequence is: MDDSTEREQS RLTSCLKKRE EMKLKECVSI LPRKESPSVR SSKDGKLLAA TLLLALLSCC LTVVSFYQVA ALQGDLASLR AELQGHHAEK LPAGAGAPKA GLEEAPAVTA GLKIFEPPAP GEGNSSQNSR NKRAVQGPEE TVTQDCLQLI ADSETPTIQK GSYTFVPWLL SFKRGSALEE KENKILVKET GYFFIYGQVL YTDKTYAMGH LIQRKKVHVF GDELSLVTLF RCIQNMPETL PNNSCYSAGI AKLEEGDELQ LAIPRENAQI SLDGDVTFFG ALKLL wherein B lymphocytes are inhibited.	This claim is the Proposed Count.
196. A method of inhibiting B lymphocyte proliferation comprising administering an effective amount of an antibody that binds Neutrokine-alpha (SEQ ID NO:2), wherein B lymphocyte proliferation is inhibited.	This claim would be anticipated and/or rendered obvious by the Proposed Count because it was well known in the art at the time the invention was made that: • B lymphocytes, when activated, undergo proliferation (growth) and differentiation (maturation) into antibody producing (immunoglobulin producing) B cells. *See, e.g.*, Janeway, C. & P. Travers. *Immunobiology: The Immune System in Health and Disease*, (Current Biology Ltd./Garland Publishing, London) 1994; pp. 3:38 and 8:2 (legend to Figure 8.1) (Appendix M); and Abbas, A.K. *et al.*, *Cellular and Molecular Immunology,* (W.B. Saunders Company, Harcourt Brace Jovanovich, Inc., Philadelphia) 1991. pp. 187 and 189 (Appendix N). Accordingly, the method of inhibiting B lymphocytes in the Proposed Count anticipates and/or renders obvious the methods of inhibiting B lymphocyte proliferation and differentiation recited in

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
	the claims of the present application. • the amino acid sequence of Neutrokine-alpha (SEQ ID NO:2) is identical to the amino acid sequence recited in the Proposed Count (see Appendix O). • because Neutrokine-alpha and the protein recited in the Proposed Count are the same molecule, an "antibody that binds Neutrokine-alpha (SEQ ID NO:2)" is interchangeable with an "an antibody that binds a protein whose amino acid sequence is: MDDSTEREQS RLTSCLKKRE EMKLKECVSI LPRKESPSVR SSKDGKLLAA TLLLALLSCC LTVVSFYQVA ALQGDLASLR AELQGHHAEK LPAGAGAPKA GLEEAPAVTA GLKIFEPPAP GEGNSSQNSR NKRAVQGPEE TVTQDCLQLI ADSETPTIQK GSYTFVPWLL SFKRGSALEE KENKILVKET GYFFIYGQVL YTDKTYAMGH LIQRKKVHVF GDELSLVTLF RCIQNMPETL PNNSCYSAGI AKLEEGDELQ LAIPRENAQI SLDGDVTFFG ALKLL". Thus, because all of the limitations recited in Claim 196 of the present application would either be anticipated or rendered obvious by the Proposed Count, Claim 196 corresponds to the Proposed Count.
197. A method of inhibiting B lymphocyte differentiation comprising administering an effective amount of an antibody that binds Neutrokine-alpha (SEQ ID NO:2), wherein B lymphocyte differentiation is inhibited.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claim 196. Thus, because all of the limitations recited in Claim 197 of the present application would either be anticipated or rendered obvious by the Proposed Count, Claim 197 corresponds to the Proposed Count.
198. The method of any one of claims 195-197, wherein the antibody is a monoclonal antibody.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197, and in addition, because methods of making and using monoclonal antibodies

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
	were well known in the art at the time the invention was made, as acknowledged by Biogen in the '605 Patent. *See, '605 Patent, col. 11, lines 4-8* ("Antiprotein/anti-peptide antisera or monoclonal antibodies can be made by standard laboratory protocols (See, for example, *Antibodies, A Laboratory Manual* ed. by Harlow and Lane (Cold Spring Harbor Press: 1988)"). Accordingly, it would have been obvious to use the monoclonal antibody of Claim 198 in the recited method in view of the Proposed Count, and therefore, Claim 198 corresponds to the Proposed Count.
199. The method of any one of claims 195-197, wherein the antibody is recombinantly produced.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197, and in addition, because methods of making and using recombinantly produced antibodies, including chimeric antibodies and antibodies comprising human constant domains, were well known in the art at the time the invention was made, as acknowledged by Biogen in its '605 Patent. *See, '605 Patent, col. 11, line 66 - col. 12, line 8* ("Various forms of antibodies can also be made using standard recombinant DNA techniques. Winter and Milstein (1991) *Nature* 349:293-299, specifically incorporated by reference herein. For example, chimeric antibodies can be constructed in which the antigen binding domain from an animal antibody is linked to a human constant domain (e.g. Cabilly et al., U.S. Pat. No. 4,816,567, incorporated herein by reference). Chimeric antibodies may reduce the observed immunogenic responses elicited by animal antibodies when used in human clinical treatments."). More specifically, the Winter and Milstein

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
	reference described above, a copy of which is attached as Appendix P, teaches that on or before its publication date of January 24, 1991, it was within the ordinary skill in the art to use recombinant DNA techniques ("gene technology") to make chimeric antibodies, humanized antibodies, antibodies with human constant domains and Fab fragments, (see, e.g., Winter and Milstein at p. 293, Figure 2 and its legend on page 295, p. 296, 3rd and 4th full paragraphs). Accordingly, it would have been obvious to use the recombinantly produced antibody of Claim 199 in the recited method in view of the Proposed Count, and therefore Claim 199 corresponds to the Proposed Count.
200. The method of any one of claims 195-197, wherein the antibody is a chimeric antibody.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197 and 199. Accordingly, it would have been obvious to use the chimeric antibody of Claim 200 in the recited method in view of the Proposed Count, and therefore, Claim 200 corresponds to the Proposed Count.
201. The method of any one of claims 195-197, wherein the antibody is a humanized antibody.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197 and 199. Accordingly, it would have been obvious to use the humanized antibody of Claim 201 in the recited method in view of the Proposed Count, and therefore Claim 201 corresponds to the Proposed Count.
202. The method of any one of claims 195-197, wherein the antibody comprises human constant domains.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
	195-197 and 199. Accordingly, it would have been obvious to use the antibody comprising human constant domains of Claim 202 in the recited method in view of the Proposed Count, and therefore, Claim 202 corresponds to the Proposed Count.
203. The method of any one of claims 195-197, wherein the antibody is a $F(ab')_2$ fragment.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197 and 199, and in addition, because methods of making and using $F(ab')_2$ fragments were well known in the art at the time the invention was made, as acknowledged by Biogen. *See, '605 Patent, col. 11, lines 50-56* ("The term antibody was used herein is intended to include fragments thereof which are also specifically reactive with BAFF-ligand, or its receptors. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. For example, $F(ab')_2$ fragments can be generated by treating antibody with pepsin."). *See also*, Janeway, C. & P. Travers. *Immunobiology: The Immune System in Health and Disease*, (Current Biology Ltd./Garland Publishing, London) 1994. p. 3:5 (Appendix M). Figure 3.4 on page 3:5 of *Immunobiology* shows that both Fab and $F(ab')_2$ fragments were well known to those of skill in the art at the time the invention was made. Accordingly, it would have been obvious to use an antibody that is an $F(ab')_2$ fragment of Claim 203 in the recited method in view of the Proposed Count, and therefore, Claim 203 corresponds to the Proposed Count.
204. The method of any one of claims 195-197,	This claim would be anticipated and/or

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
wherein the antibody is a polyclonal antibody.	rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197, and in addition, because methods of making and using polyclonal antibodies were well known in the art at the time the invention was made, as acknowledged by Biogen in the '605 Patent. *See, '605 Patent, col. 11, lines 4-8* ("Antiprotein/anti-peptide antisera or monoclonal antibodies can be made by standard laboratory protocols (See, for example, *Antibodies, A Laboratory Manual* ed. by Harlow and Lane (Cold Spring Harbor Press: 1988)"). More specifically, the Harlow reference described above, a portion of which is attached as Appendix Q, teaches that on or before its publication date (1998) it was within the ordinary skill in the art to make antisera containing polyclonal antibodies. (*See, e.g.*, Harlow at p. 115) *See also* Golub, E.S. and D.R. Green, *Immunology: A Synthesis* (Sinauer Associates, Inc. Sunderland, MA) 1991; p. 134 (a copy of which is attached hereto as Appendix R), which teaches that "The response of the individual to the whole antigen is therefore POLYCLONAL, but the response of each B cell is MONOCLONAL. A 'conventional' antiserum...almost always has antibodies directed against many determinants on the antibody molecule. In other words, conventional antisera are both multispecific and polyclonal." Accordingly, it would have been obvious to use the polyclonal antibody of Claim 204 in the recited method in view of the Proposed Count, and therefore, Claim 204 corresponds to the Proposed Count.
205. The method of any one of claims 195-197, wherein the antibody is a Fab fragment.	This claim would be anticipated and/or rendered obvious by the Proposed Count for

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
	the same reasons explained above for Claims 195-197 and 199. Accordingly, it would have been obvious to use the antibody that is an Fab fragment of Claim 205 in the recited method in view of the Proposed Count, and therefore, Claim 205 corresponds to the Proposed Count.
206. The method of any one of claims 195-197, wherein the antibody is administered to an individual.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197, and in addition, because methods of administration of an antibody to an individual were well known in the art at the time the invention was made, as acknowledged by Biogen in its '605 Patent. *See, '605 Patent, col. 4, lines 44-49 and col. 5, lines 45-49* ("the present invention is directed to the use of BAFF-ligands, blocking agents and antibodies for the ligand, to either stimulate or inhibit the growth of B-cells and the secretion of immunoglobulin. The claimed invention may be used for therapeutic applications in numerous diseases and disorders") *and col. 5, lines 45-49*("The pharmaceutical preparations of the invention may, optionally, include pharmaceutically acceptable carriers, adjuvants, fillers, or other pharmaceutical compositions, and may be administered in any of the numerous forms or routes known in the art."); *see also* Waldmann, TA, (2003) "Immunotherapy: Past, Present and Future" *Nature Medicine* 9:269-277, a copy of which is attached hereto as Appendix T. Box 5 of Waldmann shows that prior to the earliest filing date of the present application, two monoclonal antibodies had already been approved for administration to humans by the United States Food and Drug Administration. Accordingly, it would have been obvious to

Claims of the Present Application	Reason Claim Corresponds to Proposed Count
	administer the claimed antibody to an individual in the recited method in view of the Proposed Count, and therefore, Claim 206 corresponds to the Proposed Count.
207. The method of any one of claims 195-197, wherein the antibody is administered to a cell culture.	This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 195-197, and in addition, because methods of administration of an antibody to a cell culture were well known in the art at the time the invention was made. See, for example, Otten et al., (1989) "Nerve growth factor induces growth and differentiation of human B lymphocytes" *Proceedings of the National Academy of Sciences, USA* 86:10059-10063 (Appendix S), particularly section entitled "Effect of NGF on T- and B-Cell proliferation commencing on p. 10060. Otten et al. demonstrate the administration of an antibody to a cell culture containing B lymphocytes, to inhibit the proliferation of said B lymphocytes. Accordingly, it would have been obvious to administer the claimed antibody to a cell culture in the recited method in view of the Proposed Count, and therefore, Claim 207 corresponds to the Proposed Count.